EXHIBIT A

Critical Reviews™ in Therapeutic Drug Carrier Systems, 21(6):433–475 (2004)

Orally Fast Disintegrating Tablets: Developments, Technologies, Taste-Masking and Clinical Studies

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ABSTRACT: Fast disintegrating tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation resulted in development of several FDT technologies. This review describes various formulations and technologies developed to achieve fast dissolution/dispersion of tablets in the oral cavity. In particular, this review describes in detail FDT technologies based on lyophilization, molding, sublimation, and compaction, as well as approaches to enhancing the FDT properties, such as spray-drying, moisture treatment, sintering, and use of sugar-based disintegrants. In addition, taste-masking technologies, experimental measurements of disintegration times, and clinical studies are also discussed.

KEY WORDS: fast dissolving, fast disintegrating, fast melting, taste masking, disintegration time, clinical studies

I. INTRODUCTION

I.A. Dysphagia and Fast Disintegrating Tablets (FDTs)

Dysphagia, or difficulty in swallowing, is common among all age groups.[1] According to a study by Sastry et al.,[2]dysphagia is common in about 35% of the general

0743-4863/04$20.00

population, as well as an additional 30–40% of elderly institutionalized patients and 18–22% of all persons in long-term care facilities. Common complaints about the difficulty in swallowing tablets in the order of frequency of complaints are size, surface, form, and taste of tablets. Geriatric and pediatric patients and traveling patients who may not have ready access to water are most in need of easy swallowing dosage forms.[2] Another study shows that an estimated 50% of the population suffers from this problem. These studies show an urgent need for a new dosage form that can improve patient compliance.[3] Solid dosage forms that can be dissolved or suspended with water in the mouth for easy swallowing are highly desirable for the pediatric and geriatric population, as well as other patients who prefer the convenience of readily administered dosage forms.[4]

During the last decade, fast disintegrating tablet (FDT) technologies that make tablets disintegrate in the mouth without chewing and additional water intake have drawn a great deal of attention. The FDT is also known as *fast melting, fast dispersing, rapid dissolve, rapid melt,* and/or *quick disintegrating tablet.* All FDTs approved by the Food and Drug Administration (FDA) are classified as orally disintegrating tablets. Recently, the European Pharmacopeia adopted the term *orodispersible tablet* for a tablet that disperses or disintegrates in less than 3 minutes in the mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients. The disintegration time for good FDTs varies from several seconds to about a minute.

I.B. Advantages of FDTs

FDTs have all the advantages of solid dosage forms, such as good stability, accurate dosing, easy manufacturing, small packaging size, and easy handling by patients.[3,5-7] FDTs also have the advantages of liquid formulations, such as easy administration and no risk of suffocation resulting from physical obstruction by a dosage form. The primary patients for FDTs are pediatric, geriatric, and bedridden or developmentally disabled patients; patients with persistent nausea; and patients who have little or no access to water. Application of FDTs can of course be extended to more general patients of daily medication regimens. From the pharmaceutical industry's point of view, FDTs can provide new dosage forms as a life cycle management tool for drugs near the end of their patent life.

Because the tablets disintegrate inside the mouth, drugs may be absorbed in the buccal, pharyngeal, and gastric regions. Thus, rapid drug therapy intervention and increased bioavailability of drugs are possible. Because the pre-gastric drug absorption avoids the first-pass metabolism, the drug dose can be reduced if a significant amount of the drug is lost through the hepatic metabolism.

II. DESIRED CHARACTERISTICS AND DEVELOPMENT CHALLENGES OF FDTS

Because administration of FDTs is different from administration of conventional tablets, the FDTs should maintain several unique properties, as listed below.[3,4,8]

II.A. Fast Disintegration

FDTs should disintegrate in the mouth without additional water or with a very small amount (e.g., 1–2 mL) of water. The disintegration fluid is provided by the saliva of the patient. The disintegrated tablet should become a soft paste or liquid suspension, which can provide good mouth feel and smooth swallowing. The "fast disintegration" usually means disintegration of tablets in less than 1 minute, but it is preferred to have disintegration as soon as possible.

II.B. Taste of Active Ingredients

Because FDTs dissolve or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds. After swallowing, there should be minimal or no residue in the mouth. A pleasant taste inside the mouth becomes critical for patient acceptance. Unless the drug is tasteless or does not have an undesirable taste, taste-masking techniques should be used. An ideal taste-masking technology should provide drugs without grittiness and with good mouth feel. The amount of taste-masking materials used in the dosage forms should be kept as low as possible to avoid excessive increase in tablet size. The taste-masking technology should also be compatible with FDT formulations. For example, if drug particles are coated to minimize unpleasant taste, the coating should not be broken during compression or dissolved during wet granulation. Taste masking of bitter-tasting drugs is critical to the success of the FDT formulations.

II.C. Drug Properties

For the ideal FDT technology, the drug properties should not significantly affect the tablet property. Many drug properties could potentially affect the performance of FDTs. For example, the solubility, crystal morphology, particle size, hygroscopicity, compressibility, and bulk density of a drug can significantly affect the final tablet's characteristics, such as tablet strength and disintegration. The FDT technology should be versatile enough to accommodate unique properties of each drug.

II.D. Tablet Strength and Porosity

Because FDTs are designed to have a quick dissolution/disintegration time, the tablet porosity is usually maximized to ensure fast water absorption into the tablets. The key properties of the tablets are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires that excipients should have high wettability, and the tablet structure should also have a highly porous network. Because the strength of a tablet is related to compression pressure, and porosity is inversely related to compression pressure, it is important to find the porosity that allows fast water absorption while maintaining high mechanical strength. In addition, low compression pressure causes fast dissolving dosage forms to be soft, friable, and unsuitable for packaging in conventional blisters or bottles. A strategy to increase tablet mechanical strength without sacrificing tablet porosity or requiring a special packaging to handle fragile tablets should be provided.

II.E. Moisture Sensitivity

FDTs should have low sensitivity to humidity. This problem can be especially challenging because many highly water-soluble excipients are used in formulation to enhance fast dissolving properties as well as to create good mouth feel. Those highly water-soluble excipients are susceptible to moisture; some will even deliquesce at high humidity. A good package design or other strategy should be created to protect FDTs from various environmental conditions.[8]

III. FORMULATION PROCESSES FOR MAKING FAST-DISSOLVING TABLETS

There are several technologies that produce commercially available FDTs. Zydis® (Cardinal Health, Dublin, Ohio), OraSolv®/DuraSolv® (Cima Labs, Eden Prairie, Minnesota), and WOWTAB® (Yamanouchi Pharma Technologies, Norman, Oklahoma) are widely known technologies (Table 1). Some of the FDT products on the market are listed in Table 2. Although these technologies meet the special requirements for FDTs to some extent, none has all the desired properties. The currently available technologies have been reviewed in the literature.[2,4,5,9] The technologies are usually grouped according to the method used in making FDTs, such as freeze drying, molding, and compression; compression is the most widely used method for making FDTs. Some methods are focused on unique granulation methods,

TABLE 1. Summary of Technologies Used to Prepare FDTs

Basis for Technology	Company	Technology
Lyophilization process	Cardinal Health	Zydis®
	Janssen Pharmaceutica	Quicksolv®
	Pharmalyoc	Lyoc®
	Elan	NanoCrystal™
Cotton candy process	Biovail (Fuisz)	FlashDose®
Tableting process	Cima Labs	OraSolv®/DuraSolv®
	Yamanouchi	WOWTAB®
	Elan Corp.	Fast Melt®
	Ethypharm	Flashtab®
	Eurand	AdvaTab™/Ziplets®
	KV Pharmaceutical	OraQuick®
	SPI Pharma	Pharmburst™
	Akina	Frosta®

such as spray-drying and flash-heating, to make shear form formulations; some are focused on selecting specific excipients such as water-insoluble calcium salt, specific disintegrant combination, and specific sugar combination; and some are focused on special treatment after compression, such as sublimation, sintering, and humidity treatments. Each method is examined in more detail below.

III.A. Freeze Drying

Freeze drying (lyophilization) is a process in which solvent is removed from a frozen drug solution or a suspension containing structure-forming excipients. The resulting tablets are usually very light and have highly porous structures that allow rapid dissolution or disintegration. When placed on the tongue, the freeze dried unit dissolves almost instantly to release the incorporated drug. The entire freeze drying process is done at nonelevated temperatures to eliminate adverse thermal effects that may affect drug stability during processing. When stored in a dried state, the freeze-dried dosage form has relatively few stability problems during its shelf life. The freeze-drying process may result in a glassy amorphous structure of excipients as well as the drug substance, leading to the enhanced dissolution rate. Freeze drying, however, is a relatively expensive manufacturing process, and the formulation has poor stability at higher temperature and humidity.[5]

TABLE 2. Examples of Commercially Available, Preapproval, or Submitted Orally Disintegrating Tablet Products

Brand name	Active ingredient	Application	Company	Technology
Claritin® RediTabs®	Loratadine	Antihistamine	Schering Corporation	Zydis®
Feldene Melt®	Piroxicam	NSAID	Pfizer	
Maxalt®-MLT®	Rizatritpan benzoate	Migrane	Merck	
Pepcid® ODT	Famotidine	Anti-ulcer	Merck	
Zyprexa®	Olanzapine	Psychotic disorders	Eli Lilly	
Zofran® ODT®	Ondansetron	Anti-emetic	Glaxo Smith Kline	
Risperdal® M-Tab™	Risperidone	Schizophrenia	Janssen	
Zubrin™(pet drug)	Tepoxalin	Canine NSAID	Schering Corporation	
Zelapar™	Selegiline	Parkinson's disease	Elan / Amarin Corporation	
Klonopin® Wafers	Clonazepam	Sedation	Roche	
Children's Dimetapp® ND	Loratadine	Allergy	Wyeth Consumer Healthcare	
Imodium Instant Melts	Loperamide HCl	Anti-diarrheal	Jannsen	
Propulsid® Quicksolv®	Cisapride monohydrate	Gastrointestinal prokinetic agent	Janssen	Quicksolv®
Tempra Quicklets Tempra FirsTabs	Acetaminophen	Analgesic	Bristol-Myers Squibb	OraSolv®
Remeron® SolTab®	Mirtazapine	Anti-depression	Organon Inc.	
Triaminic® Softchews®	Various combinations	Pediatric cold, cough and allergy	Novartis Consumer Health	

Brand name	Active ingredient	Application	Company	Technology
Zomig-ZMT® and Rapimelt®	Zolmitriptan	Anti-migraine	AstraZeneca	DuraSolv®
Alavert®	Loratadine	Allergy	Wyeth Consumer Healthcare	
NuLev®	Hyoscyamine sulfate	Anti-ulcer	Schwarz Pharma	
Kemstro™	Baclofen	Anti-spastic analgesic	Schwarz Pharma	
Benadryl® Fastmelt®	Diphenhydramine citrate	Allergy, sinus pressure relief	Pfizer	WOWTAB®
Nasea OD	Ramosetoron HCl	Anti-emetic	Yamanouchi	
Gaster D	Famotidine	Anti-ulcer	Yamanouchi	
Excedrin® QuickTabs	Acetaminophen	Pain reliever	Bristol-Myers Squibb	QuickTabs™
Ralivia FlashDose®	Tramadol HCl	Analgesics	Biovail	FlashDose®
Zolpidem ODT	Zolpidem tartrate	Sleep disorders	Biovail	
Fluoxetine ODT	Fluoxetine	Anti-depression	Biovail	
Nurofen® Flashtab®	Ibuprofen	NSAID	Boots Healthcare	Flashtab®
Hyoscyamine Sulfate ODT	Hyoscyamine sulfate	Anti-ulcer	ETHEX Corporation	OraQuick
Cibalginadue FAST	Ibuprofen	NSAID	Novartis Consumer Health	Ziplets™

The Zydis® technology is the most well known example of the freeze drying method. In the Zydis® formulations, the drug is physically trapped in a matrix composed of two components, a saccharide (e.g., mannitol) and a polymer.[10-12] The carrier polymers commonly used in the Zydis® system include (partially hydrolyzed) gelatin, hydrolyzed dextran, dextrin, alginates, poly(vinyl alcohol), polyvinylpyrrolidone, acacia, and mixtures thereof. After the solution or dispersion is filled into blister cavities, it is then frozen in a liquid nitrogen freezing tunnel. The solvent in the frozen state is removed to produce porous wafers. Because the units are fragile and light-weight, they cannot withstand thea pressure of being pushed through the foil of a conventional blister. A special peelable backing foil is used to package the Zydis® units. Because the water content in the final freeze-dried product is too low for microbes to grow, the Zydis® formulation is also self-preserving.[3] However, the Zydis® formulation is so sensitive to moisture that the tablet may melt between sweaty fingers when it is taken out of the package. This dosage form may degrade at humidity greater than 65%, so a pinhole or minor damage to the package will lead to collapse of the tablet.[9]

There are some requirements for the Zydis® technology. The drug should be chemically stable and water insoluble, with a particle size smaller than 50 μm. Precipitation may occur during manufacturing if large drug particles are used. The water soluble drugs may form eutectic mixtures that cannot be frozen adequately to form the rigid structure necessary to support itself after solvent is removed, which may cause collapse of the freeze dried cake. For this reason, the dose for water-soluble drugs is usually limited to 60 mg[3]. Higher drug dosing can be accommodated without losing the rapid disintegration property, however, if a thickened (i.e., paste-like) form of an oil-in-water emulsion is directly placed in the blister cell.[13]

There are 13 products currently available based on the Zydis® technology. The products on the US market include Claritin® Reditab®, Dimetapp® Quick Dissolve, Feldene® Melt, Maxalt-MLT®, Pepcid® RPD, Zofran® ODT®, and Zyprexa® Zydis®. In the worldwide market, oxazepam, lorazepam, loperamide, and enalapril are available in the Zydis® formulations (Table 2).[9]

Quicksolv® (Janssen Pharmaceutica, Beese, Belgium) and Lyoc® (Farmalyoc Laboratorie L., Lefon, Maisons-Alfort, France) are also prepared by the freeze-drying method. In the Quicksolv® formulation, the matrix compositions are dissolved in the first solvent (usually water), and then the solution is frozen. At the temperature at which the first solvent will remain in the solid form, the frozen solution contacts the second solvent, which is substantially miscible with the first solvent. For example, ethanol, menthol, or acetone is used as the second solvent with water as the first solvent. The matrix composition should be immiscible to the second solvent. Thus, the first solvent is substantially removed after a few hours of contacting the second solvent, resulting in a usable matrix.[14] The final product disintegrates almost instantly. This method is claimed to prevent or reduce the

incidence of cracking during the final preparation, having uniform porosity and adequate strength for handling.

In the Lyoc® formulation, the porous solid form is obtained by freeze drying an oil-in-water emulsion placed directly in the blister pockets.[13] In order to prevent inhomogeneity by sedimentation during freeze drying, this formulation requires a large proportion of undissolved inert filler to increase the viscosity of the suspension. The high proportion of filler reduces the porosity of the tablet, and as a result, the disintegration is slower. It is also noted that the tablet still has poor mechanical resistance.

NanoCrystal™ technology (Elan, King of Prussia, Pennsylvania) uses orally administered nanoparticles (<2 μm) in the form of rapidly disintegrating tablet matrix. The NanoCrystal™ orally disintegrating tablet dosage form was developed to facilitate the preparation of small-scale clinical supplies. NanoCrystal™ colloidal dispersions of drug substance are combined with water-soluble ingredients, filled into blisters, and lyophilized. This approach is especially attractive when working with highly potent or hazardous materials because it avoids manufacturing operations such as granulation, blending, and tableting, which generate large quantities of aerosolized powder and present much higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into FDTs because manufacturing losses are negligible. The final tablet is durable enough for conventional blister or bottle packaging and accepts as much as 200 mg of drug per unit. Other features include conventional, compendial inactive components and non–moisture-sensitive inactive ingredients.[15]

III.B. Molding

The major components of molded tablets typically are water-soluble ingredients. The powder mixture is moistened with a solvent (usually ethanol or water), and then the mixture is molded into tablets under pressures lower than those used in conventional tablet compression. (This process is known as *compression molding.*) Then the solvent can be removed by air-drying. Because molded tablets are usually compressed at a lower pressure than are conventional compressed tablets, a higher porous structure is created to enhance the dissolution. To improve the dissolution rate, the powder blend usually has to be passed through a very fine screen.

Recently, the molded forms have also been prepared directly from a molten matrix in which the drug is dissolved or dispersed (known as *heat molding*) or by evaporating the solvent from a drug solution or suspension at ambient pressure (*no-vacuum lyophilization*).[4] Solid dispersion also can be used to make the tablets. The drug can remain discrete particles or microparticles dispersed in the matrix. It can dissolve totally in the molten carrier to produce a solid solution or dissolve partially

in the molten carrier while the remaining undissolved particles disperse in the matrix. The characteristics of the tablets (such as disintegration time, drug dissolution rate, and mouth feel) vary based on the type of the dispersion or dissolution.

Because of their water-soluble sugar components, molded tablets disintegrate more rapidly and offer improved taste. However, molded tablets typically do not have great mechanical strength.[16] The chance of erosion and breakage of the molded tablets during tablet handling and opening blister pockets is high. If hardness-enhancing agents are added to the formulation, the rate of tablet disintegration usually decreases.

Mechanical strength and good disintegration of the tablets can be improved by using nonconventional equipment and/or multistep processes. Using a nonconventional approach, however, requires substantially larger investment in machinery. Compared with freeze-drying, molded tablets can be produced more simply and efficiently at an industrial scale, although disintegration times may not be comparable to those of lyophilized forms.

Takeda Chemical Industries (Osaka, Japan) and Nippon Shinyaku (Kyoto, Japan) have disclosed compression-molding.[17,18] The wetted mass was compressed at low pressure and subsequently dried to produce porous tablets with sufficient mechanical strength. The disintegration time was about 30–50 seconds in the mouth. In a patent by Novartis Consumer Health (Basel, Switzerland), the drug solution or suspension was dispersed into molds. The solvent was removed from the units usually by heating, pressure reduction, or microwave radiation.[19] In a patent by Okada, the molded tablets contained a drug, a saccharide having a solubility of 30 (w/w)% or less at room temperature (e.g., lactose and mannitol), and a saccharide having a solubility of 30 (w/w)% or more at room temperature (e.g., glucose, fructose, sucrose, xylose, trehalose, xylitol, sorbitol, erythritol, dextrin, and pullulan). The amount of this saccharide was slightly above its solubility. The mixture was a creamy aqueous suspension having both low solubility and high solubility saccharides in water. The moisture was then removed from the suspension to obtain molded tablets.[20] Pebley et al. described a vacuum drying process.[21] The matrix network of the tablet included a gum, a carbohydrate, and the drug. Vacuum drying of the tablet above its collapse temperature instead of freeze drying below its collapse temperature provides a process for producing tablets with enhanced structural integrity, while rapidly disintegrating in normal amounts of saliva.

Bi et al. studied the factors that affect tablet properties in the wet compression method.[22] Lactose with various particle sizes was wetted and compressed at low compression forces. The resulting wet mass was dried in a circulating-air oven. The result suggested that the tablet strength and disintegration time were related to the amount of solid bridges formed between lactose particles. By optimizing factors such as compression force, size of lactose particles, and moisture content of the granules, which may affect solid bridge formation, tablets with tensile strength greater than

0.5 MPa and disintegration time shorter than 15 seconds could be made by the wet compression method.

III.C. Compaction

Using a conventional tablet press to make fast-dissolving tablets is a very attractive method because of the low manufacturing cost and ease in technology transfer. However, the tablet press has been designed to make conventional tablets. When making conventional tablets, maintaining high tablet porosity is not a primary concern, and high compression force is used to ensure the tablet strength. Many strategies have been tried to achieve high porosity and adequate tablet strength using a tablet press. First, several granulation methods have been tried to obtain granules suitable for making FDTs. Wet granulation, dry granulation, spray drying, and flash heating methods have been tried. The second approach is to select special types of excipients as the main component for FDTs. The third approach is to compress tablets at low pressure and apply various after-treatments to the soft tablets. The three most widely used approaches are described in detail below.

1. Granulation Methods

a. Wet Granulation

Bonadeo et al. described a process of producing FDTs by wet granulation in a fluidized bed.[23] It was found that even with effervescent agents presented in the tablet with lower than 5%, quick disintegration times could be achieved. Furthermore, it was also found that fast disintegration time could be achieved using only the acid component of the effervescent couple. In the patent, the formulation includes polyalcohols (e.g., mannitol, xylitol, sorbitol, maltitol, erythritol, and lactitol), 1–30% of an edible acid, and an active ingredient as the dry mixture. This mixture was wet granulated with an aqueous solution of a water-soluble or water-dispersible polymer (e.g., poly(ethylene glycols), carrageenan, and ethylcellulose), which consisted of 1–10% of the final weight of the granule in a fluid bed. Granules with high porosity and low apparent density were obtained, and the tablets made by such granules had rapid disintegration times ranging from 3 to 30 seconds in the saliva.

Jian et al.[24] developed an FDT for a poorly water-soluble active ingredient. First, nanoparticles were formed by mechanical grinding, precipitation, or any other suitable size reduction process. Those nanoparticles, less than 2 μm, were stabilized by surfactants. The particles were granulated with at least one pharmaceutically acceptable water-soluble or water-dispersible excipient using a fluid bed, and the

granules were made into tablets. The tablets had complete disintegration or dissolution in less than 3 minutes.

b. Dry Granulation

Eoga and Valia[25] disclosed a method of making FDTs by dry granulation. Higher density alkali earth metal salts and water-soluble carbohydrates usually do not provide quick disintegration and a smooth mouth feel. Low-density alkali earth metal salts and water soluble carbohydrates are also difficult to compress and caused inadequate content uniformity. For these reasons, low-density alkali earth metal salts or water-soluble carbohydrates were precompacted, and the resulting granules were compressed into tablets that could dissolve fast. In this process, a powdered material with a density of 0.2–0.55 g/mL was precompacted to increase the density to 0.4–0.75 g/mL by applying a force ranging from 1 to 9 kN/cm. The resulting granules were compressed into tablets.

c. Melt Granulation

Abdelbary et al.[26] described a new approach of preparing FDTs with sufficient mechanical strength, involving the use of a hydrophilic waxy binder (Superpolystate®, PEG-6-stearate) by melt granulation or wet granulation. Because Superpolystate® is a waxy material with a melting point of 33–37 °C and a hydrophilic to lipid balance (HLB) value of 9, it will not only act as a binder and increase the physical strength of tablets but also help the disintegration of the tablets. In case of melt granulation, granules were prepared in a high-speed blade mixer at 40–44 °C, according to the conventional hot-melt procedure. For wet granulation, an oil-in-water emulsion of Superpolystate® was used as the granulating agent. Then, granules were blended with croscarmellose, aspartame, and magnesium stearate and compressed into tablets. The melt granulation FDTs had better hardness results than the wet granulation FDTs. The disintegration times of melt granulation tablets, however, was more than 1 minute.

d. Spray Drying

Spray drying methods are widely used in pharmaceutical and biochemical processes. Spray drying provides a fast and economical way of removing solvents and producing highly porous, fine powders. Allen and Wang[27] produced a particulate support matrix for use in making FDTs by a spray-drying technique. The compo-

nents included supporting agents composed of two polypeptide components of the same net charge (preferably nonhydrolyzed and hydrolyzed gelatin), a bulking agent (mannitol), and a volatilizing agent. To maintain the net charges of the polypeptide components, an acidifying or alkalinizing agent was included. The mixtures of the above components were spray dried to obtain porous granules. The reason to use polypeptide components of the same charge was that molecules would repel each other even after spray drying, so porous and low-bulk-density particles could be formed. By incorporating a volatilizing agent (ethanol in most cases), the surface tension of the droplets was further reduced during spray drying, and more pores and channels were created. The dissolution rate of the matrix was further increased when combined with a bulking agent. A minimal amount of an effervescent agent was optionally included to further accelerate the dissolution rate. To aid in keeping the tablets intact during handling, a thin coating of polymeric material could be applied externally. This coating should not inhibit the capillary uptake of water during dissolution. Active ingredients can be microencapsulated or nanoencapsulated to further achieve taste masking.

e. Flash Heat Process

Fuisz Technologies (Chantilly, Virginia) has introduced the Shearform® technology to make Flashdose. The Shearform® technology[28] uses a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. In this process, the feedstock is subjected to centrifugal force and to a temperature gradient simultaneously. An internal flow is created by this condition to force the flowing mass out of the opening provided in the perimeter of a spinning head. The mass is cooled down as it comes out of the opening to form a discrete fiber structure, as seen in cotton candy. The speed of spinning is about 3,000–4000 rpm, and the temperature gradient is about 180–250°C. The carrier materials include saccharides, polysaccharides, and mixtures thereof.

There were two systems used to create the Shearform® technology floss that has self-binding properties.[29,30] The first system was named a *single floss* or *unifloss*. Typical flosses of this kind, made of sucrose, sorbitol, and xylitol, yielded effective self-binding properties. The second system used two separate flosses. One was xylitol-containing binder flosses and the other was base flosses that contain different sugar alcohols or saccharide. When the two flosses were combined, it was termed a *dual floss* system.

The produced floss needed to be recrystallized to form freely flowing granules with self-binding properties. Two techniques were used in recrystallization. One was using crystallization enhancers including ethanol, polyvinylpyrrolidone, water (e.g., moisture), glycerin, and radiant energy (e.g., microwaves). The other was using

crystallization modifiers, which were included in floss ingredients at 0.01–20.0% the weight of the floss. Typical crystallization modifiers were surfactants having an HLB of about 6 or more.

A hygroscopic material such as xylitol must be present in the system to provide good self-binding characteristics to the final matrices. In order to produce and control the self-binding properties, this hygroscopic material must have a substantially higher hygroscopicity than that of the carrier carbohydrate (e.g., sucrose). The initial floss coming out of the spinning machine is in its amorphous state. However, because of its tendency to pick up moisture and induce crystallization by crystallization enhancers or modifiers, the floss recrystallizes into a more crystalline structure. Because of intimate contacts among all components in the matrix, recrystallization of one component can have significant impact on the characteristics of surrounding components and further change the properties of the matrix as a whole. The floss gradually loses its amorphous character as the recrystallization continues. The flowability of the floss is enhanced to make it suitable for the conventional tableting process.

2. Direct Compression

From the pharmaceutical manufacturer's point of view, direct compression is the simplest and most cost-effective tablet manufacturing procedure. Pharmaceutical companies can use conventional manufacturing equipment and commonly available ingredients. This method can be applied to manufacturing FDTs by choosing appropriate combinations of excipients, which can provide fast disintegration and good physical resistance. Sugar-based excipients have been widely used as bulking agents because of their high aqueous solubility and sweetness, pleasing mouth-feel and good taste masking. Nearly all formulations for FDTs incorporate some sugar materials in their formulations.[8]

a. Disintegrants Used in FDTs

Some patents use effervescent couples as their disintegrant, while others use a combination of disintegrants. Dobetti[6] summarized different types of non-effervescent disintegrants used in the pharmaceutical area.

- ***Starch and modified starches.*** This group includes natural starches (such as maize starch and potato starch), directly compressible starches (such as starch 1500), modified starches (such as carboxymethylstarches and sodium starch glycolate), and starch derivatives (such as amylose).

- ***Cross-linked polyvinylpyrrolidone***
- ***Modified celluloses*** such as cross-linked sodium carboxymethylcellulose
- ***Alginic acid and sodium alginate***
- ***Microcrystalline cellulose***
- ***Methacrylic acid-divinylbenzene copolymer salts***

In addition, poly(acrylic acid) superporous hydrogel (SPH) microparticles were recently reported as superdisintegrants possessing a unique porous structure.[31] They were used as a wicking agent to decrease the disintegration time of FDTs. The poly(acrylic acid) SPH microparticles can swell approximately 80 times in distilled water and 50 times in pH 6.8 0.2 M phosphate buffer. The SPH microparticle size had a significant effect on the disintegration time and tensile strength of ketoprofen FDTs. The minimum disintegration time was observed when the microparticle size was in the range of 75–106 μm. Tensile strength of the tablets decreased as the SPH microparticle sizes decreased from 180–250 μm to 25–44 μm. However, when the microparticle sizes were smaller than 25 μm, the tensile strength of the resultant tablets increased as the size decreased. The optimal microparticle size should be in the range of 75–106 μm. The FDTs made of SPH microparticles in the range of 75-106 μm showed the fastest disintegration time (15.0 ± 2.0 s) and higher tensile strength (84.4 ± 4.1 N/cm^2).

b. Inorganic Excipients Used in FDTs

Dobetti[6] has developed a formulation using insoluble inorganic excipients as the main component for FDTs. According to the patent, disintegration of a tablet depends on the quantity of the disintegrant and insoluble inorganic excipient used. The disintegration also depends on the relative weight ratio between the water insoluble and soluble excipients, if the water-soluble excipients are used. It was also found that in their formulations, sufficient compression could be applied to form tablets with strong tensile strength and low friability. The disintegration rates were not significantly affected by the high compression force. In the formulation, three major components were used:

- ***Substantially water insoluble components.*** This group includes water-insoluble excipients, water-insoluble drugs (either coated or uncoated), and water-insoluble lubricant and glidant. The water-insoluble excipients include insoluble inorganic

salt (e.g., di- or tri-basic calcium phosphate) or organic filler (e.g., microcrystalline cellulose).

- ***Substantially soluble components.*** This group includes compressible sugars, flavoring agents, sweeteners, binders, and surfactants.

- ***Disintegrants.*** Examples are maize starch or modified starch, cross-linked polyvinylpyrrolidone, or sodium carboxymethylcellulose.

The disintegration time increased as the amount of insoluble component decreased. If the active ingredient was only a small portion of the whole formulation, the disintegration time could be optimized by including insoluble fillers (e.g., microcrystalline cellulose and silicon dioxide) or by increasing the amount of insoluble inorganic excipients (e.g., calcium salt such as dibasic calcium phosphate).

3. Compaction and Subsequent Treatments

a. Sublimation

The slow dissolution of the compressed tablet containing even highly water-soluble ingredients is due to the fact that the low porosity of the tablets reduces water penetration into the matrix. When volatile materials are compressed into tablets using the conventional method, they can be removed via sublimation, resulting in highly porous structures. The volatile materials include urea, ammonium carbonate, ammonium bicarbonate, hexa methylene tetramine, and camphor. Heinemann[32] disclosed a process to prepare porous tablets by sublimation. The mixtures of volatile adjuvants were made into tablets, which were subsequently heated to remove the volatile adjuvants. Roser and Blair[33] used vacuum to remove the volatile materials. The full dissolution time was reduced from 10–15 minutes for the tablets formed from trehalose alone to less than 1 minute. In some cases, menthol, camphor, thymol, an organic acid such as adipic acid, and a lower fatty acid such as arachidic acid, capric acid, myristic acid, and palmitic acid were used as the volatile materials,[34] and the sublimation temperature ranged from 40 to 60 °C. The disintegration time in the human mouth was claimed to be about 25 seconds.

Lo[35] disclosed an efficient method for preparing high-strength, highly porous, fast-dissolving delivery devices. In this method menthol, a water-soluble, menthol-soluble polymer, and an active ingredient are mixed at a temperature that insures that the menthol is substantially molten. The formulation is disposed in a mold and solidified, and the menthol is sublimed from the solidified molded formulation. Pref-

erably, the solidification occurs at a temperature sufficient to provide a substantially amorphous menthol structure.

b. Humidity Treatment

The mechanical strength of some tablets increased substantially after moisture treatment, compared with the tablets before the treatment. The increase is known to be due to the formation of liquid bridges in the presence of moisture and then formation of solid bridges after drying. As shown in Figure 1, when solid particles start to pick up moisture from the atmosphere, the water is adsorbed onto the surface (A), and then water molecules form a film on it with the vapor pressure over the adsorbed moisture layer equal to P_b (B). The solid starts to dissolve into the adsorbed moisture layer, and the dissolution of solid in the adsorbed moisture will lead to a decrease in the vapor pressure P_b (C). The decrease in P_b is effectively offset by the increase in temperature of the film (and the solid) caused by the heat released on condensation of the water vapor. The moisture sorption occurs spontaneously, and the thickness of the condensate film grows as long as $P_a > P_b$. The solid continues to dissolve and saturate the film, maintaining the vapor pressure over the adsorbed moisture layer (P_b). After drying, a solid bridge is believed to occur and increase bonding between the particles (D).

It is also known that certain types of sugar change from the amorphous to the crystalline state when their solution is spray dried or used as a binder solution. Further investigations have shown that when an amorphous sugar is treated to go through the humidification and drying process, it changes to a crystalline state. This change increases the tablet strength substantially.[36,37] The conceptual process of structural changes of amorphous sucrose to crystalline sucrose is shown in Figure 2.

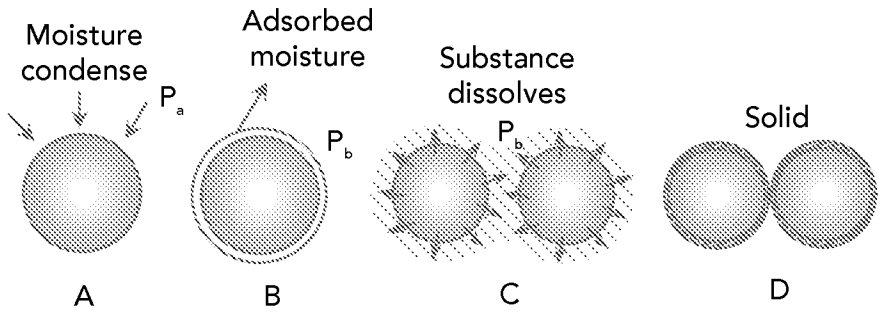

FIGURE 1. A moisture sorption model explaining the increase mechanical strength of FDTs.

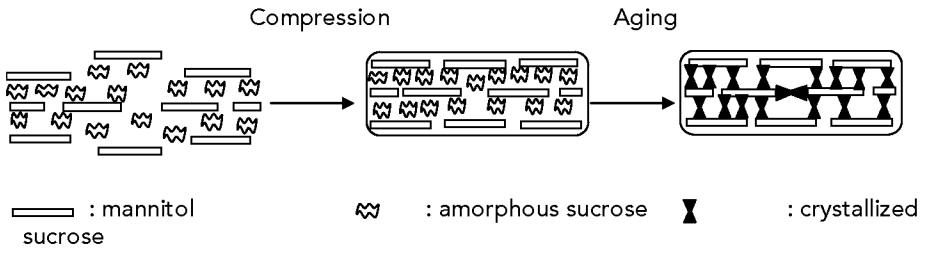

FIGURE 2. A model describing the increase in tablet strength by transformation of amorphous sucrose to crystalline sucrose upon storing under a certain relative humidity. (Adapted from Reference 36).

In a patent by Mizumoto et al.,[37] a drug, a sugar, and an amorphous sugar capable of transforming from amorphous to crystalline state were mixed and compressed into tablets. After the tablets were formed, they were humidified and dried. The amount of the sugar in the formulation can be adjusted according to the drug content and tablet size. The "amorphous sugars" are those that can form an amorphous state by spray drying, freeze drying, or other granulation methods. These amorphous sugars include glucose, lactose, maltose, sorbitol, trehalose, lactitol, and fructose. The relative humidity is determined by the apparent critical relative humidity of the mixture of a drug and an amorphous sugar. A relative humidity greater than or equal to the critical relative humidity of this mixture is chosen for the humidity condition. The advantage of using amorphous sugars is that they have low critical relative humidity, so that they can absorb water even at low moisture levels. The crystalline form of the sugars has difficulty in controlling moisture absorption. Moisture absorption of the crystalline form is not sufficient to strengthen the tablets at a low humidity condition. If a high humidity condition is used, tablets may adhere together, causing manufacturing problems. Another advantage of using amorphous sugars is that transformation of the amorphous state to the crystalline state is irreversible. The sugars in crystalline state have a high critical moisture point, so the strengthened tablets are less susceptible to moisture.

Liu et al.[38] disclosed a system for making FDTs by humidity treatment. The process includes the following steps: (1) a water-soluble polymer was used as a binder solution to granulate active ingredients and other excipients, such as low-modability sugars; (2) the granules were then compressed into tablets; (3) the tablets were humidified at relative humidity of about 50–100%; and (4) the tablets were dried. The hardness of the tablet was about 0.5–12.0 kilopounds, and the in vivo disintegration time was claimed to be about 1–40 seconds.

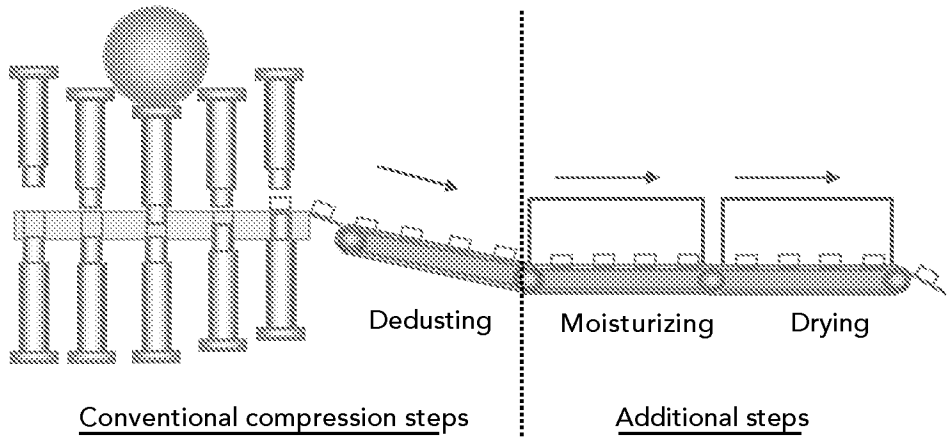

FIGURE 3. Schematic view of the manufacturing apparatus using moisture treatment.[39] The left side of a dotted line shows the conventional compression and dedusting steps, while the right side shows the additional step requiring special chambers for moisture treatment and drying.

Tatara et al.[39] also used moisture treatment and devised an apparatus to handle the fragile tablets before moisture treatment. An active ingredient and other excipients were compressed in low pressure, and then the resultant tablets were moisturized and dried to produce a porosity between 20 and 40%. As shown in Figure 3, the manufacturing apparatus includes a rotary punch-press, a relay conveyor for transferring tablets, a moisturizing section, a drying section, and a delivery conveyor. In the moisturizing section, the condition was set to allow tablets moisturized at 45 °C, 95% relative humidity for 60 seconds. In the drying section, the temperature was set to 50 °C for 60 seconds. With this apparatus the fragile tablets before moisture treatment were gently transferred throughout the process.

c. Sintering

Lagoviyer et al.[40] disclosed a process that increased tablet strength by sintering the tablet components at high temperatures and then resolidifying them at lower temperatures. The components in this formulation include bulk agents, structure agents, solvent, and binding agents. A bulk agent in this formulation is used to provide bulk volume to the overall tablet, and suitable agents include carbohydrates, calcium carbonate, and magnesium carbonate. The suitable structure agents should provide

a porous support structure to allow quick dissolution of the tablets in the mouth. The structural agents include agar, gelatin, albumin, and chondroitin. Bulking and structural agents were dissolved in a suitable solvent, and the dissolved mixture was spray dried or dispersed to obtain a bead or granulated product with a low density. Choice of the solvent is based on its ability to provide a desired porosity to the bead or granulated product upon drying. Solvents can be chosen from water, ethyl alcohol, isopropyl alcohol, or a mixture thereof.

The binders need to melt at the sintering stage, form bonding among granules, and resolidify as the temperature of the final sintering or heating step decreases. Binders are water soluble polymers such as poly(ethylene glycol) (PEG), with a molecular weight of approximately 1000 to 1,000,000. PEG melts at 50–90 °C. PEG has the advantage of functioning both as a binder and as a capillary attractant. The amount of binding polymer ranged from 0.5% to 25% of the weight of the final product.

The binding agents and active ingredients can be introduced to the formulation in several ways. A binding agent and active ingredient can also be dry blended to the spray-dried or dispersed granulated product. They can alternatively be dissolved into solvent with bulking agent and spray dried into granules. The granules are then lightly compressed to form tablets. These tablets are heated for a sufficient time and temperature to allow the binding agent to melt. The heating step is intended to melt the binding agent to create intra-tablet bonds and help weld the product shape together. Typically, a laboratory oven is set at around 50–100 °C. The heating time ranges from 3 to 45 minutes. The binding agents are resolidified as the temperature is reduced to ambient temperature. The disintegration time is generally within 3–60 seconds.

The heat treatment or sintering step in the patent improved the product's strength and durability. Because the active ingredient can be introduced into the formulation in several ways, taste-masking technologies can be easily incorporated into the process. The dosage form allows the incorporation of a wide range of dosage levels. Because of the high temperature treatment, when heat-labile drugs are incorporated in the formulation, careful attention should be given in this process.

The advantages and disadvantages of the technologies describe here are summarized in Table 3. These technologies are commonly applied yo the production and development of FDTs.

IV. FDT FORMULATION EXAMPLES

Because the direct compression is most desirable in terms of producing FDTs with high mechanical strength, ease of manufacturing, and low cost, currently available FDT formulations using direct compression are described in detail.

TABLE 3. Comparison of Technologies for Preparing FDTs

Technology	Advantages	Disadvantages
Freeze drying	Immediate dissolution (2–10 s)	Very poor physical resistance High cost of production Sensitive to humidity Low dose of water-soluble drugs
Molding	Very rapid dissolution (5–15 s) High dose	High cost of production Weak mechanical strength Possible limitations in stability
Tableting (standard)	Low cost of production Use of standard equipment/ materials High dose Good physical resistance	Significant effects of the size and hardness of the tablets on disintegration property
Tableting (effervescent)	Use of standard equipment High dose Good physical resistance Pleasant effervescent mouth feel	Operating in controlled low humidity Need of totally impermeable blister
Tableting (Humidity Treatment)	Good physical resistance Pleasant mouth feel	Extra equipments for humidification and drying Possible limitations in stability High cost of production Not suitable for moisture sensitive compounds Fragile before humidity treatment
Tableting (sublimation)	Good physical resistance	Harmful residual adjuvants Extra equipments for heating Not applicable to volatile and heat sensitive drugs

IV.A. OraSolv® and DuraSolv® Technology

OraSolv® technology (Cima Labs) produces tablets by low compression pressure.[41,42] It uses an effervescent disintegration pair that releases gas upon contact with water. The widely used effervescent disintegration pairs usually include an acid source and a carbonate source. The acid sources include citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, and succinic acids. The carbonate sources include sodium bicarbonate, sodium carbonate, potassium bicarbonate, and potassium carbonate. The carbon dioxide evolved from the reaction may provide some "fizzing" sensation,

which is a positive organoleptic sensation. The amount of effervescent agent is in general about 20–25% of the total weight of the tablet.

Because of the soft and fragile nature of OraSolv® tablets, a special packaging system, known as PakSolv®, was developed to protect the tablets from breaking during transport and storage.[43] PakSolv® is a "dome-shaped" blister package that prevents the vertical movement of the tablet within the depressions, because the diameter of the lower portion of the dome is too narrow to accommodate the tablet. PakSolv® also offers light, moisture, and child resistance.

As a second-generation technology, the DuraSolv® technology was developed by Ciba to provide stronger tablets for packaging in blisters or bottles.[44] The key ingredients in this formulation are nondirect compression filler and lubricant. The particle size of the nondirect compression filler is preferably between about 20 and 65 μm, while for direct compressible fillers at least 85% of the particles are over 100 μm in size. These nondirect compression fillers, such as dextrose, mannitol, sorbitol, lactose, and sucrose, have the advantage of quick dissolution and avoid some of the gritty or sandy texture usually present in direct compressible versions of the sugar. The amount of a nondirect compression filler is usually about 60–95% of the total tablet weight. The tablets have low friability, which is about 2% or less when tested according to the USP, and the hardness of the tablets is at least about 15–20 N. The disintegration time is less than 60 seconds.

It is interesting to note that in comparison with the conventional tablet formulations, higher amounts of hydrophobic lubricants, such as magnesium stearate, can be added to the formulation with nondirect compression fillers as the main component. About 1–2.5% of lubricant can be added to the formulation, compared with 0.2–1% of lubricant in conventional tablets. The lubricant blending times can also be increased to 10–25 minutes or longer. Relatively modest compressive force is needed to compress the formulation. This method can produce tablets by the direct compression method and use conventional tableting methodologies and conventional package equipment. Thus, the production cost is significantly decreased.

IV.B. WOWTAB® Technology

WOWTAB® technology employs a combination of low- and high-moldability saccharides to produce fast-dissolving tablets using conventional granulation and tableting techniques.[37,45] According to the patent, saccharides were divided into two groups: those with high moldability and those with low moldability. Low-moldability saccharides produce tablets with hardness between 0 and 2 kg, when

150 mg of such a saccharide is compressed under pressure of 10–50 kg/cm^2 using a die 8 mm in diameter. The typical low-moldability saccharides include lactose, mannitol, glucose, sucrose, and xylitol. High-moldability saccharides produce tablets with hardness above 2 kg when prepared under the identical conditions. The typical high-moldability saccharides are maltose, maltitol, sorbitol, and oligosaccharides.

When tablets are made by compressing a saccharide having low moldability or high moldability alone, the desired properties of adequate hardness and quick disintegration in the mouth cannot be achieved simultaneously. Moreover, if saccharides having low moldability and high moldability are mixed (physical mixture) before tableting, quick disintegration and dissolution in the mouth cannot be obtained. As clearly indicated in the patents, there is no single saccharide that can make tablets having both high strength and fast disintegration properties. For this reason, a saccharide having low moldability was granulated with a saccharide having high moldability as a binder. The low-moldability saccharides were used as the main component. Tablets made by compression of these granules were further treated under moisture condition as described in Figure 3. The tablets show an adequate hardness and fast disintegration and dissolution when put in the mouth.

IV.C. Flashtab® Technology

Flashtab® technology (Ethypharm, France) produces tablets by compression of granular excipients.[46] This technology uses almost the same excipients as do conventional compressed tablets. Excipients used in this technology comprise two groups of components: disintegrating agents, such as carboxymethylcellulose or insoluble reticulated polyvinylpyrrolidone; and swelling agents, such as carboxymethylcellulose, starch, modified starch, carboxymethylated starch, microcrystalline cellulose, and possibly directly compressible sugars. The mixture of excipients is prepared by either dry or wet granulation methods. The produced tablets are known to have satisfactory physical resistance and disintegrate in the mouth within 1 minute.

IV.D. AdvaTab™ Technology

AdvaTab™ technology (Eurand) produces FDT tablets based on a proprietary tablet composition that was designed and patented by Kyowa Hakko Kogyo (Tokyo, Japan),[47,48] in which the lubrication is dispensed onto each tablet by using

a spray during the production process. Traditional tablets are produced using an internal lubrication system, which disperses lubricant on the inside and the surface of the tablets. This method can decrease tablet mechanical strength. AdvaTab™ is produced using 10–30 times less hydrophobic lubricant and can be 30–40% stronger than conventional tablets. As a result, the tablets are hard and durable yet do not impede liquid entry upon contact with saliva. AdvaTab™ can handle high drug loading and coated drug particles. Importantly, the technology does not require specialty packaging and, as a result, can be packaged in both standard bottles and push-through blisters.

IV.E. Dispersible Tablet Technology

Lek[50] in Yugoslavia was issued patents for dispersible tablets of dihydroergotoxine[49] and cimetidine, which were claimed to disintegrate in less than 1 minute when in contact with water at room temperature. Dihydroergotoxine is poorly soluble in water in the free base form. An improved dissolution rate of dihydroergotoxine methanesulphonate was observed with dispersible tablets containing 0.8–10%, preferably about 4% by weight, of an organic acids. One of the essential excipients in the cimetidine formulation was a disintegrating agent. It provides rapid swelling and/or good wetting capability to the tablets and thereby a quick disintegration. The disintegrating agents include starch or modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxymethyl cellulose, and cyclodextrin polymers. A combination of two or more disintegrating agents produced better disintegration results.

IV.F. Pharmaburst™ Technology

Pharmaburst technology™ (SPI Pharma, New Castle, Delaware) uses off-the-shelf coprocessed excipients to create an FDT that, depending on the type of active ingredient and loading (up to 700 mg), dissolves within 30–40 seconds. The quantity of Pharmaburst™ required in a formulation depends on the active ingredient in the tablet. It is necessary to carry out initial studies on a formulation by varying the amount of Pharmaburst™ from 50 to 80%, depending on the desired mouth feel and disintegration time. The process involves a dry blend of a drug, flavor, and lubricant that are compressed into tablets on a standard tablet press with stock tooling. The manufacture process can be carried out under normal temperature and humanity conditions. The tablets can be packaged in blister packs or bottle.[15]

IV.G. Frosta® Technology

The core concept of Frosta® technology is compressing highly plastic granules at low pressure to produce strong tablets with high porosity. The highly plastic granules comprise three classes of components: a porous and plastic material, a water penetration enhancer, and a binder. The highly plastic granules can then be compressed at low pressure to form a fast-melting pharmaceutical tablet. A porous, plastic material is water soluble or water dispersible, sometimes almost instantaneously upon contact with water. Plastic deformation of powders dramatically increases the chance of the interparticle contacts necessary to form bonds between particles. If a porous and plastic material is polymeric, it is essential to prevent formation of a viscous layer of the material at the tablet surface when it dissolves in aqueous medium. One way of making such tablets is to mix porous, plastic material with a water penetration enhancer at certain ratios. In this process, the porous and plastic particles are separated by water-penetration-enhancing particles, which prevent formation of a viscous layer on the tablet surface. Although the porous and plastic materials can make close contacts to increase the chance of bonding by compression, formation of really strong bonding among granules at low pressures requires a suitable binder. The binder here can also secure the porous material and water penetration enhancer during granulation. These two components can be easily segregated during mixing without the binder. If the binder is in the liquid or semi-solid state, it should not significantly destroy the porous structure of the porous materials. One way of achieving this is to use aqueous binder solutions with very low water activity. The highly plastic granule approach produces FDTs with excellent hardness and fast disintegration time ranging from several seconds to about 30 seconds, depending on the size of the tablets.

IV.H. SEM Pictures of FDTs Prepared by Direct Compression

FDTs prepared by direct compression disintegrate or melt in the mouth, and the disintegration time ranges from several seconds to about 1 minute, depending on the size of FDTs and the preparation method. Figure 4 shows SEM pictures of several samples of FDTs. Figure 4A shows a picture of a highly porous inner structure of Claritin® RediTabs® prepared by freeze drying. This is a typical freeze-dried structure that can result in immediate disintegration and dissolving of the tablet on the tongue. Such highly porous structure also explains why they are very fragile. Figure 4B shows an inner structure of Alavert™, which is an effervescent tablet containing Loratadine. It is made by direct compression, and so the structure is much different from that prepared by freeze drying. Figure 4C shows an inner structure of a

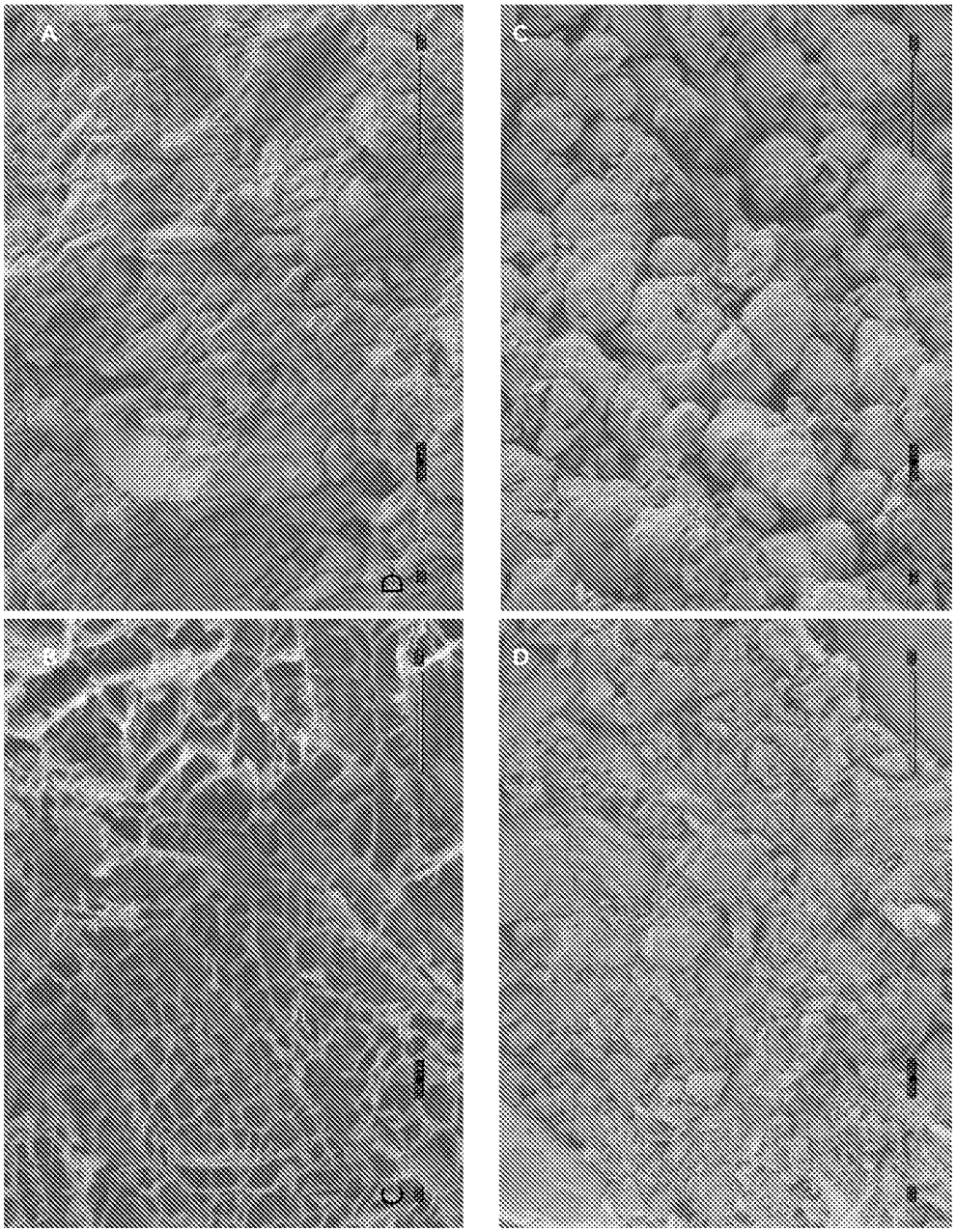

FIGURE 4. Scanning electron microscopic pictures of a selected number of FDTs. Claritin™ RediTabs™ **(A)**, Alavert™ **(B)**, Benadryl™ Fastmelt™ **(C)**, and Frosta™ vitamin B12/folic acid **(D)**. The scale bar is 100 μm.

Benadryl®Fastmelt™, which used WOWTAB® technology. Compared with Figure 4A, the porosity of tablets prepared by direct compression is much lower, but the tablet strength is much higher. Figure 4D shows an inner structure of a Frosta tablet containing vitamin B12 and folic acid. In this approach, highly plastic granules are compressed to form a tablet. As shown in the figure, there are empty spaces between granules where water can be absorbed by capillary force. The granules are then easily dissociated, and the whole tablet melts to form a paste that is easy to swallow. Figure 4 shows that FDTs prepared by direct compression can have porous structures made of granules, and the disintegration time can be very short as a result of fast absorption of water by capillary force.

V. TASTE MASKING

It is estimated that there are about 10,000 taste buds on the tongue, roof of the mouth, cheeks, and throat, and each bud has 60–100 receptor cells. These receptor cells interact with molecules dissolved in the saliva and produce a positive or negative taste sensation. Many drugs are unpalatable and unattractive in their natural state. Physiological and physicochemical approaches have been used to prevent drugs from interacting with taste buds, and thus to eliminate or reduce negative sensory response.[51]

After FDTs disintegrate/dissolve in the saliva, the drug in FDTs remains in the oral cavity until it is swallowed. If the drug has a bitter taste, taste masking is critically important in the formulation for maximal patient acceptability. Current taste masking in FDTs is achieved by using sweet-tasking substances as diluents, adding flavors, or encapsulating the unpleasant drug into microparticles or granules.

V.A. Addition of Sweeteners and Flavors

Sugar-based excipients have a negative heat of dissolution, dissolve quickly in saliva, and provide a pleasing mouth feel and good taste-masking to the final product.[8] Most of the products in the market use this kind of excipient to give pleasant mouth feeling. WOWTAB® used the so-called "smoothmelt action" of sugar and sugar-like (e.g., mannitol) excipients.[45] The Zydis® dosage form also uses sweeteners and flavors to mask an unpleasant taste.[3] In the NuLev® DuraSolv® tablet, the low dose of hyoscyamine sulfate was sufficiently taste-masked by incorporating a sweetener and a flavor.[52] Flosses and small spheres of saccharides containing unpleasant drugs were mixed with sweeteners and flavors to provide taste masking.[30,53]

V.B. Adjustment of pH Values

Many drugs are less soluble at pHs different from the pH value of the mouth, which is around 5.9. Drugs can be insufficiently solubilized to be available to taste if the equilibrium concentration is below the taste threshold.[54] After a solubilization inhibitor, such as sodium carbonate, sodium bicarbonate, sodium hydroxide, or calcium carbonate, was added to increase the pH when granules including a drug—sildenafil—dissolved in aqueous medium, the bitter taste of the drug was successfully masked by a sweetener alone.[55]

V.C. Coating or Encapsulation of Unpleasant Drugs

In some instances, sweeteners and flavors may not be sufficient to mask bitter drugs, so alternative methods of taste masking need to be employed. Frequently, the bitter-tasting drug powder is coated to inhibit or retard dissolution and solubilization of the drug. This allows time for all of the particles to be swallowed before the taste is perceived in the mouth.[54] When using a coating or encapsulation for taste masking, complete coating is necessary to prevent exposure of the taste buds to a bitter-tasting drug. It is important that the coating remain intact while the dosage form is in the mouth.

The process of Microcaps® (Eurand) is also based on a microencapsulation technology—i.e., deposition of a polymeric membrane on drug particles. This deposition is typically carried out in a liquid phase using the technique known as phase separation or coacervation. This process is also very useful in obtaining microcapsules for delayed or controlled release applications, in addition to taste masking. The typical size of microcapsule is 0.2–0.8 mm.[56-58] The bitter taste of Linezolid was masked by a combination of microencapsulation by coacervation and subsequent functional membrane coating on the microcapsules with Eudragit L30D.[59] Small particles such as crystals, granules, and pellets were coated with aqueous dispersions of methacrylic acid and methacrylic ester copolymers (Eudragit RL 30D, RS 30D, L 30 D-55, and NE 30D) for taste masking and compressed into FDTs.[60] The FDTs containing the taste-masked granules of pirenzepine HCl or oxybutynin HCl were prepared by coating the drugs with aminoalkyl methacrylate copolymers (Eudragit E100) using the extrusion method.[61] Taste-masked immediate release micromatrix powders were formed by spray drying the drug and cationic copolymer.[62]

Cima's taste-masking technology also uses coating of the active ingredient with a material that delays the dissolution in the mouth of drugs with objectionable taste.[63] Taste-masked microcapsules were prepared by a phase separation approach. First a polymeric material (water-insoluble) for microencapsulation of the drug is dissolved in a nonpolar organic solvent with a second polymeric material that pro-

motes phase separation of the first polymeric material at a temperature where both polymers dissolve. As the temperature is lowered, the first polymer forms a coating layer on the drug by phase separation, and a dispersion of microencapsulated drug is produced. After removing the solvent and the second polymeric material from the dispersion, isolated taste-masked microcapsules were obtained.[64] The mouthfeel of OraSolv® tablets is different from that of most other orally disintegrating tablets, because of the presence of an effervescent couple comprising an acidic compound and a carbonate or bicarbonate salt.

In MicroMask™ by KV Pharmaceutical, the taste-masking system was prepared by casting or spin congealing melt dispersions or solutions of a drug in a molten blend of materials. Most wax core material has a melting point within the range of 50–200 °C. The taste masking process does not use solvents of any kind, and therefore leads to faster and more efficient production.[65] Bite-dispersion tablets were prepared using a waxy material and phospholipid.[66] Addition of fatty acid ester(s) and/or waxes (e.g., Witepsol H32) contributed to taste masking of drugs having an irritating taste.[67] When an active ingredient, such as acetaminophen, has a bitter taste, it can be encapsulated in a material such as partially hydrogenated cottonseed oil, corn oil, flavored oil, zein (corn protein), cellulose, or candied sugar. Encapsulation with one or more of these materials has been found to enhance the palatability of acetaminophen while the tablet is dissolving in the mouth. The tablet may also contain a flavor enhancer that further masks the taste of the drug.[21] A taste-masking composition composed of clove oil and either supportive flavor components or calcium carbonate has been found to be particularly useful for masking unpalatable active ingredients in formulations intended to be chewed or dissolve in the mouth prior to ingestion.[68]

Flashtab® technology[46] involves the use of coated multiparticles of active ingredients for effective taste-masking. Other coating techniques designed for protecting drugs can also be used for taste-masking purposes. For example, acid-labile drugs are enteric coated for protection of the drugs in the stomach. Such enteric coating can be used for taste masking, because the coating techniques should remain the same. Prevacid®SoluTab™ (TAP Pharmaceutical) is a lansoprazole delayed-release FDT for treatment and prevention of digestive ulcer.[69,70] Lansoprazole is an acid-labile drug and needs to be coated with enteric agents to prevent its release in the stomach. First, lansoprazole, a basic inorganic salt, and additives were granulated into fine granules with an average particle diameter less than 400 μm. Second, the fine granules were coated with sustained release agents. Third, the sustained release fine granules were coated with an enteric coating layer and further coated with mannitol.[71,72] It was reported that enteric-coated microgranules comprise seven layers: core, active compound layer, intermediate layer, first enteric layer, second enteric layer, third enteric layer, and over-coating layer. The enteric-coated microgranules have the multiple functions of reducing the damage to the enteric layer during

the compression process, improving the stability of lansoprazole, and masking the unpleasant bitter taste.[72,73] The enteric-coated lansoprazone microgranules can be mixed with other excipients to make the final product.

In addition to coating bitter-tasting drug particles, drugs were simply blended with cyclodextrin. Blending with cyclodextrin without the conventional complex formation was shown to be effective in masking the unpleasant-tasting active ingredients in FDTs.[74]

VI. DETERMINATION OF DISINTEGRATION TIME OF FDTS

FDTs should be strong enough to survive rough handling during manufacturing and shipping processes, and yet friable enough to instantly dissolve or disintegrate into small particles for easy swallowing by the patient. Conventional disintegration tests for ordinary tablets may not allow precise measurement of the disintegration time of FDTs because of their fast disintegration. It is also hard to distinguish among FDTs, which release their ingredients very quickly. In vitro testing may not always reflect the real in vivo disintegration of tablets.

In general, the method described in the US Pharmacopoeia can produce data for evaluation of the disintegration time; however, no additional information might be extracted. It is also possible to evaluate the tendency of the disintegration kinetics by visual examination. However, these evaluations are not sufficiently objective.[75] When developing FDT formulations, it is important to evaluate the effect of different excipients on the disintegration time. In order to predict the disintegration time of FDTs and the effects of different formulation parameters, a few methods have been proposed.[75-78] It is important to define a suitable method to better distinguish between the disintegration times of different FDTs and to find better correlation between in vitro and in vivo data. To achieve this goal, a modified dissolution apparatus was applied to FDTs with disintegration times too fast to distinguish the differences between the tablets when the conventional methods were used.[4]

VI.A. In Vivo Determination of Disintegration Time

In vivo disintegration tests of FDTs can be conducted on volunteers who are usually randomized to receive the treatments and then directed to clean their mouths with water.[78] Tablets are placed on their tongues, and the time for disintegration is measured by immediately starting a stopwatch. The volunteers are allowed to move FDTs against the upper roof of the mouth with their tongue and to cause a gentle tumbling action on the tablet without biting on it or tumbling it from side to side.

Immediately after the last noticeable granule has disintegrated, the stopwatch is stopped and the time recorded.

VI.B. In Vitro Determination of Disintegration Time

1. Modified US Pharmacopoeia Method

Instead of using the disintegration apparatus described in the US Pharmacopoeia, a modified method has been proposed.[76,77] The disintegration apparatus was the same as the USP dissolution test Apparatus 2, which uses a paddle stirring element and 1000-mL cylindrical vessel at 37 °C. Distilled water was chosen for the disintegration medium instead of a buffer solution. A tablet to be tested was put on the bottom of a sinker, which was placed in the middle of the vessel and hung by a hook to the lid of the vessel with a distance of 6–8.5 cm. Disintegration time was determined at the point at which the tablet disintegrated and passed through the screen of the sinker completely. The opening of mesh of the sinker was 3–3.5 mm in height and 3.5–4 mm in width.

2. Texture Analyzer Method

The Texture Analyzer (Stable Micro Systems, U.K.) was applied to measure the beginning and ending time of disintegration.[78] A tablet was adhered to the bottom of a probe, which was attached to the load cell with a very thin layer of glue or double-sided tape. A small amount of water, usually 0.4 mL, in a beaker or petri dish was used as a disintegration medium at room temperature. The tablet was submerged in water and compressed against the bottom of the beaker or petri dish with a constant pressure. The beaker size could be varied, and the beaker could even be a water bath to keep the temperature constant. The instrument was programmed to apply a moderate force for up to 60 seconds so that the penetration distance could be measured as the tablet was compressed while submerged in the water. The probe distance would be steady as the tablet remained cohesive. However, as the tablet disintegrated, the compression distances increased, because the probe had to keep the pressure constant. The time for the tablet to disintegrate was determined by measuring the distance the probe traveled into the tablet. Typical time-distance profiles generated by the Texture Analyzer software enabled the calculation of beginning and ending of disintegration time.

El-Arini and Clas[79] performed the in vitro disintegration test of commercially available FDTs by the Texture Analyzer instrument. The differences in the disintegration mechanisms of the FDTs, which derived from the formulation and/or

manufacturing process, were reflected in the shape of their disintegration profiles. Moreover, the in vitro disintegration times obtained by the simulated in vivo conditions were correlated with the reported in vivo disintegration times.

3. CCD Camera Method

The CCD camera apparatus comprises two distinct sections—a disintegration component and a measurement device.[75] The mode of measurement involves the continuous acquisition of pictures by the CCD camera to record the time course of disintegration. The acquired pictures are simultaneously transferred to the computer and stored. The key point of this apparatus is to combine the detailed pictures obtained by the CCD camera.

The disintegration apparatus consists of a plastic cell partitioned into two parts: one component comprises an inner tank containing a stirring bar, a grid fabricated from stainless-steel, and a disintegration medium (distilled water, 200 mL, 37 ± 2 °C); the second component is an outer tank of thermostated water. The grid is constructed of three hollow areas equidistant from the center. These hollow points represent the position of the tablets, and a support is added for each tablet to avoid movement during the disintegration test.

The CCD camera method permits documentation of the disintegration time course with sequentially obtained pictures. The computer enables calculation of the surface area of each tablet at any time point, as well as the design of graphs that show decrease in the tablet surface area as a function of time. The disintegration time and the area under the curve can be calculated from these graphs as qualitative parameters that can be correlated to the oral disintegration time. Consequently, results depend on the direction and focal length of the camera relative to the tablet. The disadvantage of the method involves difficulty associated with the application of mechanical stress to test tablets. Thus, the time required for a single test is several minutes, which is greater than that for the in vivo disintegration time.

4. Rotary-Shaft Method

FDTs generally receive some mechanical stress produced by the tongue in the human mouth. Narazaki et al.[80] developed a suitable disintegration method for FDTs. In this method, the FDT is placed on stainless steel wire gauze, which is slightly immersed in test medium, and a rotary shaft is employed to provide mechanical stress to the tablet by means of its rotation and weight. The critical parameters of this method are the rotation speed and the mechanical stress. To assess our method, several placebo FDTs were prepared and exposed to severe storage conditions (60 °C/75% RH for

1 week) in order to obtain FDTs with a wide range of disintegration times. These placebo FDTs were used to compare the disintegration times obtained by several methods, including the proposed rotary-shaft method. The disintegration time of the placebo FDTs in human sensory test varied widely after storage. The disintegration times determined by the conventional disintegration test were in good correlation to those in the human sensory test, but the slope was 0.241, far from 1. There was no correlation between the disintegration time of FDTs in the human sensory test and those determined by the conventional dissolution test. In contrast, a good correlation between the disintegration times was obtained with the new rotary-shaft method and the human sensory test, and the slope was 0.858, very close to 1. It was concluded that the proposed rotary-shaft method was suitable for the measurement of the disintegration time of FDTs. This new method might provide a valuable approach for establishing the official disintegration test for FDTs in the future.

5. Sieve Method

A simple device based on a shaking water bath was designed to measure the disintegration time of FDTs.[81] The device is composed of a 10-mesh sieve and a glass cylinder. The sieve is placed into the cylinder at a certain position so that 2 mL of disintegration medium fills the space below the sieve of the cylinder. Then, 1 mL of the medium is added into the device, so that it is available for an FDT to be tested. The device is in a reciprocal shaking water bath kept at a constant temperature of 37 °C. While the shaker is running in horizontal back-and-forth motions with 150 rpm, an FDT is placed onto the top of the sieve immersed in the disintegration medium. The FDT starts disintegration into small particles and/or dissolves, and the time at which the particles of the tablet go through the sieve completely is determined as the disintegration time. The disintegration time is measured using a stopwatch, and this quick method gives reproducible data that are highly useful in screening various formulations and testing many formulation variables.

VII. CLINICAL AND PHARMACOKINETIC STUDIES

The behavior of oral FDTs in the oral–esophageal tract, their pharmacokinetic and therapeutic efficacy, and their acceptability were investigated in in vivo studies. The investigation using gamma-scintigraphy showed that the dissolution and buccal clearance of oral fast-disintegrating dosage forms was rapid.[82] The esophageal transit time and stomach emptying time were comparable to those of traditional tablets, capsules, or liquid forms.[83,84]

VII.A. Improved Patient Compliance and Patient Convenience

FDTs are easily administrated even without water, and thus improve patient compliance and patient convenience. FDTs overcome genuine swallowing problems and prevent covert refusal to swallow in uncooperative individuals in the acute setting, potentially reducing confrontations with medical staff and improving medication compliance.[85] Sumatriptan FDTs were generally well tolerated by patients.[86] Zolmitriptan FDTs were an effective and convenient alternative to a conventional tablet, allowing migraine attacks to be treated anytime a migraine strikes, which can facilitate earlier treatment.[87-89] The FDT formulation of olanzapine, Zyprexa® Zydis®, facilitated antipsychotic medication compliance in acutely ill, noncompliant patients.[90]

VII.B. Enhanced Pregastric Absorption and Rapid Onset of Action

It has been found that FDTs can promote pregastric absorption of the active ingredients through buccal, sublingual, oropharyngeal, and esophageal membranes. Thus, FDTs can provide a rapid onset time of action required for patients, especially for those undergoing surgery and migraine. Piroxicam is known to be absorbed from the rat oral mucosa.[91] Its FDT is considered as an alternative in spine postoperative pain control during the early postoperative period,[92] the treatment of patients with acute low back pain,[93] the treatment of acute migraine,[94] and in emergency renal colic treatment[95] because of its quick onset, long duration, low side effects, and high toleration. Acetylsalicylic acid from an FDT was absorbed faster than from plain tablets, and yet the two formulations were bioequivalent with regard to absorption extent.[96] No statistical difference in C_{max} and $AUC_{0-\infty}$ between the acetaminophen FDT and the conventional tablet was observed. However, t_{max} (15 min) of the FDT was significantly ($p < 0.05$) shorter than that of the conventional tablet (130 min). The same value of t_{max} between the FDT and the solution was observed. Rapid disintegration of the tablets obviously influences the pharmacokinetics of the drug.[97] The absorption rate of the acetaminophen Flashtab® was higher than that of the brand leader, while having the same bioavailability.[98] A faster onset of action of treatment with mirtazapine FDTs was observed compared to selective serotonin reuptake inhibitor treatment.[99] With regard to efficacy in headaches, concomitant autonomic symptoms, rapid onset of effect, and acceptance, the FDT triptan formulation represents real competition with the other triptans in the usual tablet formulation.[100]

Antacids may react directly with the acid excipients in the FDT formulation to prevent the decrease in pH of the saliva, which is believed to reduce the over-

all absorption of apomorphine from the pregastric region of the gastro-intestinal tract.[101] The AUC for 10 mg apomorphine FDTs was 4.36 times higher than that of the same formulation encapsulated in a hard gelatin capsule. These results indicate that apomorphine is absorbed pregastrically from the FDTs when placed into the mouth because, when the same formulation was encapsulated (which would prevent pregastric absorption), the amount of apomorphine detected in plasma was significantly reduced. In many cases, FDTs promote pregastric absorption of the active ingredient. Dopamine agonists absorbed pregastrically pass straight into the circulatory system, thereby avoiding first-pass metabolism in the liver.[101]

VII.C. Increased Bioavailability

Increased bioavailability and side-effect reduction were observed when the drugs with marked first-pass hepatic metabolism were absorbed through the buccal and esophageal mucosa. FDTs are effective in augmenting therapeutic efficacy. Increased bioavailability and improved patient compliance were observed in Lyoc® formulations for various drugs such as phloroglucinol,[102,103] glafenine,[104] spironolactone,[103] and propyphenazone.[102,104] Zydis® selegiline can be rapidly absorbed through the oral mucosa (about 3 mg in 1 min). Selegiline bioavailability for Zydis® selegiline increased 13-fold compared with selegiline conventional tablets (Eldepryl) at the dose of 10 mg, but the metabolite bioavailability was similar for both tablets.[106] Zydis® selegiline 1.25 mg yielded similar plasma concentrations of selegiline and degree of monoamine oxidase type B (MAO-B) inhibition to conventional 10 mg selegiline tablets but markedly reduced concentrations of the principal metabolites. Thus, the lower but equally MAO-B-inhibitory dose of selegiline in Zydis® selegiline 1.25 mg, which is associated with lower concentrations of potentially harmful metabolites, could offer a safer and more predictable treatment in the management of patients with Parkinson's disease.[106] By minimizing first-pass metabolism and providing high plasma concentrations of selegiline, Zydis® selegiline at doses of 1.25 mg and 10 mg was therapeutically equivalent to conventional 10 mg selegiline tablets.[105] An efficacy and safety study showed that Zydis® selegiline safely reduced daily off time when used as adjunctive therapy with levodopa in Parkinson's disease patients.[107] Lansoprazole FDT was bioequivalent to the lansoprazole formulation, which was dispersed in water and administered orally via syringe with respect to the lansoprazole area under the plasma concentration (AUC) and C_{max}.[108] The bioavailability of lansoprazole FDT was comparable to capsules, and thus the indications and recommended dosages for the FDT were identical to the capsules.[72]

The suitability of FDTs for long-term therapy was assessed. Lyoc® formulations containing aluminum were positively tested in patients with gastrointestinal symp-

toms.[109] In vitro release of nicorandil from the FDTs containing the dry emulsions was sustained over 6 hours, while that from plain FDTs and commercial tablets was complete within 5 minutes. FDTs containing dry emulsions showed a similar AUC, lower C_{max}, and delayed t_{max} compared to the plain FDTs and commercial tablets in beagle dogs. These results suggest that the dry emulsion-loaded FDTs could be used to improve the sustained-release property of active drugs.[110]

VIII. FUTURE RESEARCH TRENDS IN FDTS

Although the FDT area has passed its infancy, as shown by a large number of commercial products on the market (as listed in Table 2), there are still many aspects to improve in the FDT formulations. Despite advances in the FDT technologies, formulation of hydrophobic drugs is still a challenge, especially when the amount of drug is high. The low dose drugs, such as Loratadine with 10 mg dose, pose little problem, but as the dose increases, the formulation sacrifices its fast disintegrating property. A new technology is being developed to incorporate higher doses of hydrophobic drugs without affecting the fast disintegrating property too severe ly. The disintegration times of most FDTs on the market are acceptable—i.e., less than 60 seconds—but certainly there is a room for improvement. Because the disintegration time is related to other formulation variables, a balance has to be maintained between shortening the disintegration time and other tablet properties. The tablet hardness, friability, and stability can be further improved to such a level that multi-tablet packaging in conventional bottles becomes a norm.

The future of FDTs lies in the development of FDTs with controlled release properties. If one FDT can deliver drugs with short half-lives for 12–24 hours, it would be a quantum improvement in the FDT technology. The added convenience and compliance of such formulations would be enormous. The future of FDTs also lies in the development of effective taste-masking properties. The use of coating poorly tasting drugs is commonly used, but it increases the total volume of the final formulation. There may be no magic solution to this, but more effective use of existing taste masking technologies is expected to alleviate the problems associated with taste masking.

In addition, the ability to formulate drugs in large doses will bring another important technological advance. In general, the FDT formulations require large amounts of excipients, and having large doses of drug will only make the final formulation too big to handle. An FDT formulations that would require fewer excipients than the drug itself would be a breakthrough. While the problems to be solved are not easy, the history suggests that it is just a matter of time before they are solved.

IX. CONCLUSIONS

The popularity of FDTs has increased tremendously over the last decade. There are about 40 drugs that have been formulated into marketed FDTs using various technologies (Table 2). The key to FDT formulations is fast disintegration, dissolution, or melting in the mouth, and this can be achieved by producing the porous structure of the tablet matrix or adding superdisintegrant and/or effervescent excipients. FDTs prepared by direct compression usually have good mechanical properties, and the strength can be enhanced further by subsequent treatment, such as moisture treatment. The clinical studies show FDTs can improve patient compliance, provide a rapid onset time of action, and increase bioavailability. Considering the many benefits of FDTs, it is only a matter of time until a majority of oral formulations are prepared in FDT forms.

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